General

Guideline Title

The Clinical Pharmacogenetics Implementation Consortium guideline for *SLCO1B1* and simvastatin-induced myopathy: 2014 update.

Bibliographic Source(s)

Ramsey LB, Johnson SG, Caudle KE, Haidar CE, Voora D, Wilke RA, Maxwell WD, McLeod HL, Krauss RM, Roden DM, Feng Q, Cooper-DeHoff RM, Gong L, Klein TE, Wadelius M, Niemi M. The Clinical Pharmacogenetics Implementation Consortium guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. Clin Pharmacol Ther. 2014 Oct;96(4):423-8. [37 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Wilke RA, Ramsey LB, Johnson SG, Maxwell WD, McLeod HL, Voora D, Krauss RM, Roden DM, Feng Q, Cooper-Dehoff RM, Gong L, Klein TE, Wadelius M, Niemi M, Clinical Pharmacogenetics Implementation Consortium (CPIC). The Clinical Pharmacogenetics Implementation Consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy. Clin Pharmacol Ther. 2012 Jul;92(1):112-7. [41 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

Genetic Test Interpretation

The assignment of the likely SLCO1B1 phenotype, based on * allele diplotypes, has been summarized in Table 1 below, based on rs4149056. *SLCO1B1* alleles are often named using * allele nomenclature, representing various single-nucleotide polymorphismsâ€‹ (SNPs) alone or in combination (http://www.pharmgkb.org/gene/PA134865839#tabview=tab4&subtab=33) (see Supplementary Table S1 online [see the "Availability of Companion Documents" field]) that are associated with low SLCO1B1 protein expression or function (see Supplementary Table S2 online [see the "Availability of Companion Documents" field]). The minor C allele at rs4149056 is contained within *SLCO1B1*5* (rs4149056 alone) as well as the **15* and **17* haplotypes and is associated with lower plasma clearance of simvastatin. The magnitude of this effect is similar for the **5*, **15*, and **17* haplotypes. *SLCO1B1* alleles have been extensively studied in multiple geographically, racially, and ethnically diverse groups. In general, rs4149056 is present at a minor allele frequency of between 5 and 20% in most populations (see Supplementary Tables S3 and S4 online [see the "Availability of Companion Documents" field]). Although all *SLCO1B1* genetic tests interrogate

rs4149056, other variants in this gene are also likely to be important, but their interpretation and application to statin prescribing is less clear. One of the limitations inherent in any genotype-only test is that very rare or *de novo* variants, which might have functional importance, will not generally be included.

Table 1. Assignment of Likely SLCO1B1 Phenotype Based on Genotype

Phenotype	Genotype Definition	Examples of Diplotypes	Genotype at rs4149056
Normal function; homozygous wild type or normal (55%–88% of patients[a])	An individual carrying two normal-function alleles	**1a/*1a, *1a/*1b, *1b/*1b*	TT
Intermediate function; heterozygous (11%–36% of patients[a])	An individual carrying one normal-function allele plus one decreased-function allele	**1a/*5, *1a/*15, *1a/*17, *1b/*5, *1b/*15, *1b/*17*	TC
Low function; homozygous variant or mutant (0%–6% of patients[a])	An individual carrying two decreased-function alleles	**5/*5, *5/*15, *5/*17, *15/*15, *15/*17, *17/*17*	CC

[a]Frequency of the polymorphism varies by ancestral group (Supplementary Tables S3 and S4 online [see the "Availability of Companion Documents" field]).

Therapeutic Recommendations

In 2011 (updated in 2013), the U.S. Food and Drug Administration (FDA) added warnings to the simvastatin product label to direct providers away from initiating at the 80-mg simvastatin dose. The agency's recommendations are further summarized in Supplementary Table S7 online (see the "Availability of Companion Documents" field). The American College of Cardiology and the American Heart Association recently issued updated clinical practice recommendations for the treatment of elevated blood cholesterol to reduce atherosclerotic cardiovascular disease, including guidelines for which patients should receive which statin at which intensity. Based on these new guidelines, it is anticipated that increasing numbers of patients will receive statin therapy; however, it is unclear as to what extent the incidence of statin-induced myopathy will also be affected. At lower simvastatin doses (e.g., 40 mg daily), it is the authors' position that *SLCO1B1* genotype (if available) could be used to warn providers about modest increases in myopathy risk for patients with a C allele at rs4149056. In these circumstances, the authors recommend a lower dose of simvastatin or use an alternative statin (e.g., pravastatin or rosuvastatin), and they also highlight the potential utility of routine creatine kinase (CK) surveillance (see Table 2, below). If patients with a C allele at rs4149056 do not achieve optimal low-density lipoprotein (LDL) cholesterol-lowering efficacy with a lower dose (e.g., 20 mg) of simvastatin, the authors recommend that the prescribing physician consider an alternate statin based on (i) potency differences (i.e., use a lower dose of a higher potency statin such as atorvastatin, rosuvastatin, or pitavastatin); (ii) drug–drug interactions (e.g., boceprevir, clarithromycin, cyclosporine, strong CYP3A4 inhibitors); and (iii) relevant comorbidities (e.g., trauma, significant renal impairment, post–solid organ transplant, thyroid disease).

At the time of this writing, there are no data available regarding *SLCO1B1* genotype effects on simvastatin response or myopathy in pediatric patients, and no data to show that the rs4149056 SNP in *SLCO1B1* affects simvastatin's disposition differently in children compared with adults.

Use of clinical decision support tools within electronic health records can assist clinicians in using genetic information to optimize drug therapy. Clinical implementation resources include workflow diagrams (see Supplementary Figures S2 and S3 online [see the "Availability of Companion Documents" field]), tables that translate genotype test results into an interpreted phenotype, example text for documentation in the electronic health record and point-of-care alerts, and cross-references for drug and gene names to widely used terminologies and standardized nomenclature systems (see Supplementary Tables S8–S12 online [see the "Availability of Companion Documents" field]).

Recommendations for Incidental Findings

Not applicable.

Table 2. Dosing Recommendations for Simvastatin Based on SLCO1B1 Phenotype

Phenotype	Implications for Simvastatin	Dosing Recommendations for Simvastatin[a,b]	Classification of Recommendations[c]

Phenotype	Implications for Simvastatin myopathy risk	Dosing Recommendations for Simvastatin[a,b]	Classification of Recommendations[c]
Normal function	Normal	Prescribe desired starting dose[b] and adjust doses of simvastatin based on disease-specific guidelines	Strong
Intermediate function	Intermediate myopathy risk	Prescribe a lower dose or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK surveillance	Strong
Low function	High myopathy risk	Prescribe a lower dose or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK surveillance	Strong

CK, creatine kinase.

[a]In all cases, the potential for drug–drug interaction should be evaluated before initiating a prescription.

[b]The U.S. Food and Drug Administration recommends against 80 mg (unless already tolerated for 12 months).

[c]See the Supplementary Material online (text section titled "Levels of Evidence" [see the "Availability of Companion Documents" field]) for additional details regarding the three-tiered system used to grade the quality of evidence.

Definitions:

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Clinical Algorithm(s)

The following algorithms are provided in the supplementary material (see the "Availability of Companion Documents" field):

- *SLCO1B1* Pharmacogenetic Test Result: Clinical Implementation Workflow for EHR
- *SLCO1B1* Genotype and Simvastatin: Point of Care Clinical Decision Support

Scope

Disease/Condition(s)

Hypercholesterolemia and cardiovascular disease

Guideline Category

Prevention

Risk Assessment

Treatment

Clinical Specialty

Cardiology

Family Practice

Internal Medicine

Medical Genetics

Pharmacology

Preventive Medicine

Intended Users

Advanced Practice Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

- To update the 2012 Clinical Pharmacogenetics Implementation Consortium guideline for *SLCO1B1* and simvastatin-induced myopathy
- To summarize the current evidence from the literature and provide therapeutic recommendations for simvastatin based on *SLCO1B1* genotype

Target Population

Patients who are on or who are being considered for simvastatin therapy

Interventions and Practices Considered

Simvastatin therapy and dosing adjustments based on *SLCO1B1* genotype or phenotype

Note: Detailed guidelines for the use of simvastatin are beyond the scope of this article.

Major Outcomes Considered

- Risk of adverse drug reactions, including statin-related muscle problems (e.g., myalgia, myopathy)
- Premature discontinuation of statin medication
- Higher low-density lipoprotein (LDL) cholesterol and cardiovascular risk

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The authors searched the PubMed database (1966 to December 2013) and Ovid MEDLINE (1950 to December 2013) using several keyword strategies: SLCO1B1, SLCO1B1 AND myopathy, SLCO1B1 AND statin myopathy, SLCO1B1 AND simvastatin, SLCO1B1 AND LDL lowering, SLCO1B1 AND statin efficacy, SLCO1B1 AND statin kinetics AND human AND polymorphism, SLCO1B1 AND cardiovascular,

OR SLCO1B1 AND statin uptake AND hepatocyte.

To construct tables showing *SLCO1B1* (1966-May 2010) minor allele frequency based on ancestry, the PubMed database was further searched using the following criteria: *SLCO1B1*, *OATP1B1*, population, rs4149056, *SLCO1B1*5*, *SLCO1B1 *15*. Studies were included if: (A) the race of the population was clearly indicated, (B) allele frequencies or minor allele percentages for *SLCO1B1* haplotypes were reported, (C) the method by which *SLCO1B1* was genotyped was reliable, (D) the sample size was at least 20 subjects.

Using the specified search criteria, 448 publications were identified (after excluding non-English manuscripts). Inclusion criteria included publications that included *in vivo* clinical outcome (i.e. lipid-lowering effects, myopathy and myalgia) for simvastatin in individuals who vary by *SLCO1B1* genotype/phenotype, associations of *SLCO1B1* genotype with simvastatin disposition in vitro, *in vivo* pharmacodynamic data for statins and *SLCO1B1* genotype/phenotype, and in vivo pharmacokinetic data for simvastatin in individuals who vary by *SLCO1B1* genotype/phenotype.

Number of Source Documents

Following application of the inclusion criteria, 25 publications were reviewed and included in the evidence table.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine the effects, but the strength of evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of the limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The evidence summarized in Supplemental Table S5 (see the "Availability of Companion Documents" field) is graded using a scale based on previously published criteria and applied to other Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. The Clinical Pharmacogenetics Implementation

Consortium (CPIC) uses a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of retroviral agents (http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf) (see the "Rating Scheme for the Strength of Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

Not stated

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Every effort was made to present evidence from high-quality studies, which provided the framework for the strength of therapeutic recommendations.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Based on the highly prevalent use of simvastatin, a potential benefit of preemptive *SLCO1B1* testing is a significant reduction in the incidence of simvastatin-induced myopathies and rhabdomyolysis, by identifying those at significant risk and recommending a lower simvastatin dose or an alternative statin as appropriate.
- In addition, genotyping may promote statin adherence and lower low-density lipoprotein (LDL) cholesterol levels.

Potential Harms

- The most common statin-related adverse drug reaction (ADR) is skeletal muscle toxicity. Statin-related muscle problems include myalgias

(pain without evidence of muscle degradation), myopathy (pain with evidence of muscle degradation), and rhabdomyolysis (severe muscle damage with acute kidney injury). Frequency varies by definition; but, overall, statin-related myalgias are common, occurring in 1% to 5% of exposed subjects.

- A possible risk could be an error in genotyping. Since genotypes are lifelong test results, any such error could stay in the medical record for the life of the patient. An error in genotyping could result in a decrease in simvastatin dose that was not otherwise necessary and could result in inadequate lipid-lowering therapy.
- Another potential risk to pre-emptive genotyping is that a patient's knowledge of a genetic profile associated with a high risk of adverse events may lead the patient to associate unrelated adverse events (i.e., nonspecific myalgias/arthralgias) to his/her statin therapy. If a patient then prematurely discontinues his/her statin and/or the physician reduces the dose, this may result in higher low-density lipoprotein (LDL) cholesterol and cardiovascular risk.

Qualifying Statements

Qualifying Statements

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written, and are intended only to assist clinicians in decision making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases that are not specifically identified. Guidelines do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health-care provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application being solely made by the clinician and the patient. CPIC assumes no responsibility for any injury to people or damage to property related to any use of CPIC's guidelines, or for any errors or omissions.

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

For the 40-mg simvastatin dose, the relative risk of myopathy is 2.6 per copy of the C allele at rs4149056. The risk is higher for the 80-mg simvastatin dose (myopathy OR 4.5 for TC genotype, ~20.0 for CC genotype). Nonetheless, simvastatin-related muscle toxicity can still occur in the absence of rs4149056. Thus, a TT genotype does not imply the absence of another potentially deleterious variant in *SLCO1B1* or elsewhere. Further, because rs4149056 can also be inherited in combination with other *SLCO1B1* gene variants known to have protective effects, it should not be presumed that the C allele at rs4149056 confers risk with 100% certainty.

Implementation of the Guideline

Description of Implementation Strategy

Use of clinical decision support tools within electronic health records (EHRs) can assist clinicians in using genetic information to optimize drug therapy. Clinical implementation resources include workflow diagrams (Supplementary Figures S2 and S3 online [see the "Availability of Companion Documents" field]), tables that translate genotype test results into an interpreted phenotype, example text for documentation in the EHR and point-of-care alerts, and cross-references for drug and gene names to widely used terminologies and standardized nomenclature systems (Supplementary Tables S8–S12 online [see the "Availability of Companion Documents" field]).

Implementation Tools

Clinical Algorithm

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Ramsey LB, Johnson SG, Caudle KE, Haidar CE, Voora D, Wilke RA, Maxwell WD, McLeod HL, Krauss RM, Roden DM, Feng Q, Cooper-DeHoff RM, Gong L, Klein TE, Wadelius M, Niemi M. The Clinical Pharmacogenetics Implementation Consortium guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. Clin Pharmacol Ther. 2014 Oct;96(4):423-8. [37 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Jul (revised 2014 Oct)

Guideline Developer(s)

Clinical Pharmacogenetics Implementation Consortium - Independent Expert Panel

Source(s) of Funding

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Guideline Committee

Not stated

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

D. Voora is a consultant for RenaissanceRx and has funding through the Department of Defense supporting an ongoing clinical trial of genotype-guided statin therapy (NCT01894230). The other authors declared no conflict of interest.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Wilke RA, Ramsey LB, Johnson SG, Maxwell WD, McLeod HL, Voora D, Krauss RM, Roden DM, Feng Q, Cooper-Dehoff RM, Gong L, Klein TE, Wadelius M, Niemi M, Clinical Pharmacogenetics Implementation Consortium (CPIC). The Clinical Pharmacogenetics Implementation Consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy. Clin Pharmacol Ther. 2012 Jul;92(1):112-7. [41 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the Pharmacogenomics Knowledgebase Web site .

Availability of Companion Documents

The following are available:

- Supplementary material, including tables and methodological information, is available from the Pharmacogenomics Knowledgebase Web site .
- Statin pharmacokinetic and pharmacodynamic pathways are available from the Pharmacogenomics Knowledgebase Web site.
- An interactive dosing table is available from the Pharmacogenomics Knowledgebase Web site .
- A 2014 SLCO1B1 translation table is available from the Pharmacogenomics Knowledgebase Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on May 15, 2013. The information was verified by the guideline developer on June 25, 2013. This summary was updated by ECRI Institute on December 4, 2014. The updated information was verified by the guideline developer on January 23, 2015.

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